Claims 1, 4, 7-9 are now pending in the application with claim 9 having been previously withdrawn. Claims 1 and 4 are currently amended. No claims are cancelled or newly added by this amendment. The Examiner is respectfully requested to reconsider and withdraw the rejections in view of the amendments and remarks contained herein.

REJECTIONS UNDER 35 U.S.C. § 112

Claims 1, 4, 7 and 8 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point and distinctly claim the subject matter which Applicants regard as the invention. These rejections are respectfully traversed.

With regard to item 2A, claims have been amended to recite that the quantitative structure activity relationship is generated for a series of molecules. In this way, the preamble of the claim is linked to the recited method steps, thereby overcoming the Examiner's concern.

With regard to items 2B and 2F, applicant maintains that the term "biological activity" is readily understood in the art and within the bounds of the pending claims. For example, biological activity can be expressed quantitatively as in the concentration of a substance required to give a certain biological response. Additionally, when physicochemical properties or structures are expressed by numbers, one can form a mathematical relationship, or quantitative structure-activity relationship, between the two. The mathematical expression can then be used to predict the biological response of other chemical structures. QSAR's most general mathematical form is:

Activity = f(physiochemical properties and/or structural properties)

The basic assumption for all molecule based hypotheses is that similar molecules have similar activities. This principle is also called Structure-Activity Relationship (SAR). The underlying problem is therefore how to define a small difference on a molecular level, since each kind of activity, e.g. reaction ability, biotransformation ability, solubility, target activity, and so on, might depend on another difference. A number of activities, not only quantitative activities such as IC_{50}, ED_{50}, BBB permeability %, but also qualitative activities such as *in vivo* drug effective class, could be used in Structure-Activity Relationship (SAR) analysis. Researchers would select the arbitral target activities from their projects. The activities used in the term "SAR" includes this concept. The present application should not be restricted for the value such as IC_{50} value, theoretically applied to all of the target activities. The applicant asserts that the term "biological activity" is readily understood to describe such activity and would be agreeable to SAR field researchers. Therefore, reconsideration and withdrawal of this objection are respectfully requested.

With regard to item 2C, applicant proposes changing the term "represented points" to "pseudo atoms" with charge = +1, and radius = 1 Angstrom. To calculate interactions on the pseudo atom position, the following equation was used. This is an example of the Gaussian-Type Evaluation Equation described in paragraph [0156] of the present application. The other evaluation equation is same as this equation.

$$A_{F,k}{}^{a}(j) = -\sum_{i=1}^{n}\left(w_{pa,k}\, w_{ik}\, e^{-ar_{iq}^{2}} \right)$$

where $A_{F,k}$ denotes an interaction between a molecule j and a pseudo atom q. the symbol W_{ik} denotes a value assigned to each physicochemical property of an atom i, where $W_{pa,k}$

denotes a value assigned to each physicochemical property of a pseudo atom. As hydrophobic parameters, parameter values in SEAL, FLEXS or HASL were applied. The pseudo atom had a charge of +1, the atomic radius of 1 angstrom and hydrophobicity of 1. The symbol α is a coefficient of an index and symbol r_{iq} denotes the distance between the pseudo atom and the point I on a molecule at which the interaction on is to be calculated. In the present invention, α is 0.3. As noted above, each pseudo atoms is defined as a charge of +1, the atomic radius of 1 angstrom and hydrophobicity of 1, atom types of the pseudo atoms are not influenced by the atom type of the removed atoms during pseudo atom generation. Thus, interactions are between atoms and/or pseudo atoms of the molecules. Interactions are in turn analyzed using regression analysis, thereby tying this step the remainder of the claimed method. Again, while applicant's method is admittedly different from standard QSAR techniques that would need to know what types of atoms make up a molecule, applicant submits that their claims accurately reflect and distinctly claim the invention. Therefore, reconsideration and withdrawal of this objection are respectfully requested.

With regard to items 2D, 2E and 2F, claims have been amended to clarify the clustering analysis of process B. Of note, the ambiguity between pseudo atoms and representative points has been resolved. Furthermore, partial least squares regression (PLS-regression) is a statistical method that bears some relation to principal components regression; instead of finding hyperplanes of maximum variance between the response and independent variables, it finds a linear regression model by projecting the predicted variables and the observable variables to a new space. Because both the X and Y data are projected to new spaces, the PLS family of methods are known as

bilinear factor models. One skilled in the art readily understands that partial least squares regression can derive a robust linear equation from tables having many more columns than rows (see, e.g., J. Am. Chem. Soc., 110, 5959-5967 (1988)). These equations are understood to be activity predicting equations and thus the claims have been amended accordingly. Moreover, a plurality of correlation coefficients can be obtained during the calculation. Therefore, reconsideration and withdrawal of these objections are respectfully requested.

With regard to item 2H, claims have been amended to clarify how the activity prediction values are assigned and displayed. Applicant notes that the region where activity will be enhanced and weakened were calculated at the positions of the pseudo atoms. Therefore, reconsideration and withdrawal of these objections are respectfully requested.

Claims 1, 4, 7 and 8 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The original CoMFA, "coefficient contour map" is generated to help in visualization. The polyhedra surrounded lattice points where the scalar products of the associated QSAR coefficient and the standard deviation of all values in the corresponding column of the data are table are higher or lower than a user-specific value. (pp. 5961, Cramer III, et al. JACS, 1998, 5959-5967).

Color is also used to code the direction and magnitude of these differential interactions. In these steric maps, blue and cyan polyhedron surround regions where more

bulk is "good" (the steric column variance-weighted QSAR coefficients are less than -0.1 in value within blue and less than -0.01 within cyan, so building is expected to increase with increases in steric bulk) while red and yellow polyhedra surrounded regions where less bulk is "good" (the steric column variance-weighted QSAR coefficients are greater than +0.1 in value within red and greater than +0.01 within yellow). The numerical data used to construct these "coefficient contour" map, the QSAR coefficients and the data table, are available in request from the authors. (pp 5962, ibid)

The present application is uses basically the same procedure to extract the "region where activity will be enhanced and weakened" such as shown in FIG. 10. The term "activity prediction of value" is "column variance-weighted QSAR coefficients" calculated by STDEV x COEFF (coefficient calculated by PLS x standard deviation associated with each column). In case of FIG. 10, 0.1 in absolute value is used to threshold for visualization of each region. Although it appears from the English translation of the application that these articles were not incorporated into the application, they do represent the knowledge base of one skilled in the art. Given this knowledge base, one skilled in the art would readily understand applicant's claimed invention from the description set forth in the application and thereby satisfy both the written description and enablement requirements.

Claims have been amended to clarify that activity prediction values are assigned at each pseudo atom position. Claims have been further amended to remove the other objectionable limitations, thereby rendering these rejections moot. For instance, "formula" was mistranslated and should have been "equation". Reconsideration and withdrawal of these objections are respectfully requested.

Claims 1, 4, 7 and 8 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement as the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. These rejections are respectfully traversed by the amendments and explanation set forth above. Reconsideration and withdrawal of these objections are respectfully requested.

CONCLUSION

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the outstanding Office Action and the present application is in condition for allowance. Thus, prompt and favorable consideration of this amendment is respectfully requested.

If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

Dated: <u>August 5, 2010</u>

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